

The response to club drug use

Jane Carlisle Maxwell

Purpose of review

Club drugs are a phenomenon that emerged during the past decade, and knowledge about them continues to evolve. The present review summarizes research published in the past year on 3,4-methylenedioxy-methamphetamine ('ecstasy'), γ -hydroxybutyrate, ketamine, and Rohypnol. These substances are described and the latest epidemiologic information is provided, and reports of patterns of use, adverse effects, pharmacology, toxicology, and management in the acute care setting are reviewed. Recent studies on the presence or absence of neurologic, psychiatric, and psychological problems related to use of these drugs are also reported.

Recent findings

An examination of the literature has shown that each of the club drugs has different properties and often different users. Each drug has different adverse effects and requires different acute care protocols. Although club drugs were identified early, scientific information about these drugs is still evolving. There are increasing numbers of studies on the short-term and long-term effects of these drugs in humans, but because of limitations on research in humans they may not always be as rigorous as desired, and can be cited by club drug users to discredit findings of harm. This has led to reliance on web-based sites that may or may not provide accurate data. Evaluated protocols for use in chemical dependency treatment for each of these drugs are still missing.

Summary

The evolving club drug phenomenon must continue to be monitored. Additional research is needed to document effects on humans and to educate clinicians on the unique properties of each drug. Research-based treatment for dependence on club drugs is needed.

Keywords

ecstasy, MDMA, GHB, ketamine, Rohypnol, club drugs

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Center for Social Work Research, University of Texas at Austin, Austin, Texas, USA

Correspondence to Jane Carlisle Maxwell, PhD, Research Scientist, Gulf Coast Addiction Technology Transfer Center, Center for Social Work Research, University of Texas at Austin, 1717 West 6th Street, Suite 335, Austin, TX 78703, USA
Tel: +1 512 263 0610; fax: +1 512 263 0613; e-mail: jcmawell@sbcglobal.net

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Abbreviations

1,4-BD	1,4-butanediol
CEWG	Community Epidemiology Work Group
CNS	central nervous system
DAWN	Drug Abuse Warning Network
GBL	γ -butyrolactone
GC-MS	gas chromatography and mass spectrometry
GHB	γ -hydroxybutyrate
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxy-methamphetamine
TCADA	Texas Commission on Alcohol and Drug Abuse

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Introduction

The illegal drug scene is changing, with the appearance of new drugs, including analogs formulated to be legal. The US National Institute on Drug Abuse, in its Community Alert on Club Drugs [1], defined club drugs as ecstasy [3,4-methylenedioxy-methamphetamine (MDMA)], γ -hydroxybutyrate (GHB), ketamine, Rohypnol (generic name flunitrazepam), methamphetamine and lysergic acid diethylamide (LSD), and described them as being used in all-night dance parties such as 'raves'. The present review looks at recent publications on MDMA, GHB, ketamine, and Rohypnol.

There have been various responses to the club drug phenomenon, and they show the problems of responding to a new epidemic. The characteristics of the drugs are summarized in the following few paragraphs, as is a brief historical background on the emergence of these agents as drugs of abuse.

Although these drugs are often considered together as 'club drugs', each has very different pharmacologic properties, physiologic and psychologic effects, and potential consequences. They are often used in combination, particularly with alcohol, but the combinations and patterns of use can be quite different. They were initially characterized as being used at raves or dance parties, but they are currently used in an expanding variety of venues by groups who differ in terms of age, sex, and race/ethnicity.

These new drugs were identified early by members of National Institute on Drug Abuse's Community Epidemiology Work Group (CEWG). Ecstasy was first reported at a CEWG meeting in 1987 [2], GHB in 1996 [3], ketamine in 1991 [4], and Rohypnol in 1993 [5]. Even with the early warnings about the emergence of these drugs, information on their pharmacology and their adverse effects has lagged behind, with the result

that front-line health workers have been handicapped in responding to them. In order to encourage research on emerging drug trends, in 2001 the National Institute on Drug Abuse issued a request for applications for epidemiologic, preventive, and health services studies relevant to emerging drug trends.

The drug scene today is impacted by the Internet, in which 'underground' websites provide thousands of pages of information on how to obtain, synthesize, extract, identify, and ingest substances [6–8] which have not been medically evaluated for dose range, effect, risk, or abuse liability [9]. At the same time, government websites contained information that was later withdrawn as more current findings emerged. (On October 25 2002, the National Institute on Drug Abuse instructed the National Clearinghouse for Alcohol and Drug Information to discontinue distributing the ecstasy brain scan poster, flier, and art card). Some antidrug sites used scare tactics and exaggerations that were ignored, whereas prodrug sites contained anecdotal or incomplete information that could lead the unaware user to increased use [10••].

Scientific studies about the uses of these club drugs and their short-term and long-term effects on humans are evolving, but because of constraints on the use of these drugs in humans, they can be subject to criticism, particularly by users, for flawed methodologies. The complexity of research on the effects on the brain can discourage reception of the findings by users and potential users, because many of the studies are difficult for nonscientists to understand.

Routine drug screens do not pick up various club drugs, and gas chromatography and mass spectrometry (GC–MS) for the specific drug must be requested. Because of the short half-life of some of the drugs, cases of sexual assault and driving under the influence have gone undetected. Improved procedures for identifying these drugs are now available.

Initially, there was little information on acute care of overdoses; needed protocols are now available. Clients citing problems with the use of club drugs are now entering substance abuse treatment programs. However, evidence-based information on treating dependence on each of these club drugs within substance abuse programs is sparse.

Groups such as DanceSafe and RaveSave have organized to reduce harm at dance parties through information about hydration status and ambient temperature, health education, drug and safe sex information, and pill testing. The response by local government in terms of enforcing fire and safety codes has varied from suppor-

tive to shutting down such venues to ignoring them, often with resulting unintended problems with crowd control and traffic jams.

Pro-rave organizations and websites have implied that only uneducated users suffer life-threatening consequences of drug use and that proper education decreases addiction. Given the scientific information that is emerging, peer-based education with a focus on both short-term dangers and long-term consequences may be a more effective approach to preventing major public health problems in the future [10••]. In addition, more emphasis on the value of these parties as places to dance and enjoy the music, rather than to 'do drugs', will be a benefit.

Ecstasy

Ecstasy (MDMA) is a synthetic, psychoactive drug with both stimulant and hallucinogenic properties similar to those of methamphetamine and mescaline. In the USA, it is a Schedule I drug.

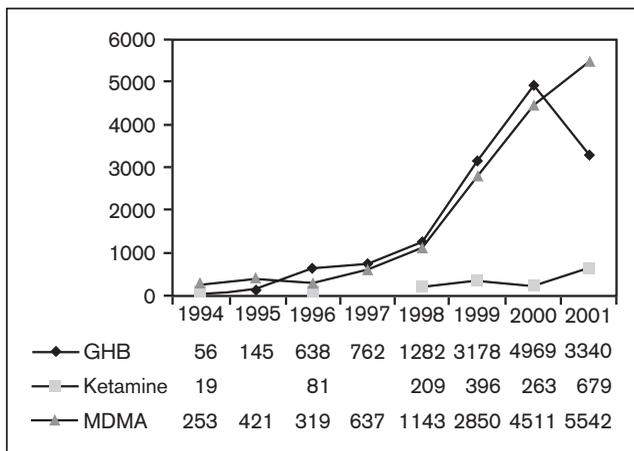
Patterns of use and formulations

In December 2001, CEWG members reported that in Atlanta, ecstasy was used with cocaine, there were reports of cutting ecstasy with OxyContin, and ecstasy use was increasing in African-American social networks. In Baltimore, variations included 'candy flipping' (mixing MDMA and LSD), 'speedballing' (MDMA and ketamine), and 'parachuting' (crushing the pill before swallowing in order to get a faster high). In Philadelphia, ecstasy was used with LSD, marijuana, or codeine cough syrup. In New York City, ecstasy use had moved from the club scene to the streets and it was being sold in powder form with cocaine or smoked in a blunt cigar filled with cannabis, or mixed with heroin and sold as 'on the ball' or 'wombstone'. Ecstasy in Boston was reported as adulterated with caffeine and its use was increasing among non-Anglo city youths [11].

Ecstasy use continues to increase. The National Household Survey on Drug Abuse [12] reported that the number of Americans aged 12 years and older who had tried ecstasy at least once in their lifetime increased from 6.5 million (2.9%) in 2000 to 8.1 million (3.6%) in 2001. The US Monitoring the Future survey [13] found that the lifetime prevalence of ecstasy use among grade 12 students rose from 6.9% in 1997 to 11.7% in 2001 and dropped to 10.5% in 2002.

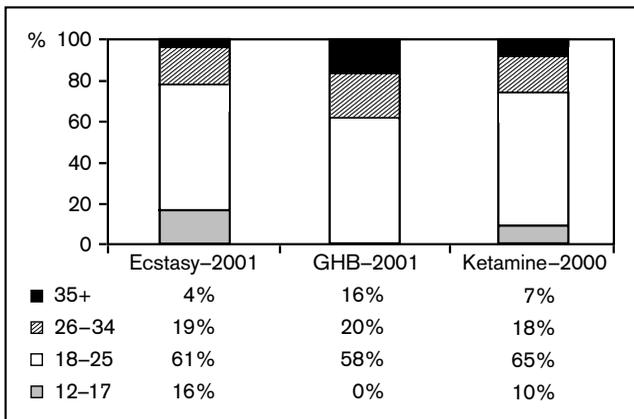
The number of mentions of ecstasy in emergency rooms monitored by the Drug Abuse Warning Network (DAWN) nationally increased from 253 in 1994 to 5542 in 2001 (Fig. 1) [14]. Patients mentioning use of ecstasy were younger than users of other club drugs (Fig. 2).

Figure 1. Drug Abuse Warning Network emergency department mentions of selected club drugs for the coterminous US: 1994–2001



GHB, γ -hydroxybutyrate; MDMA, 3,4-methylenedioxy-methamphetamine (ecstasy).

Figure 2. Age groups of patients mentioning specific drugs in Drug Abuse Warning Network emergency departments



GHB, γ -hydroxybutyrate.

Fifty-six per cent were male, 63% were Anglo, 12% were African-American, and 9% were Hispanic. Eighty-six per cent mentioned MDMA in combination with other drugs, which included alcohol (48%), marijuana (33%), cocaine (29%), LSD (8%), heroin (8%), GHB (7%), ketamine (5%), methamphetamine (5%), and amphetamine (4%).

Ecstasy use is often reported at ‘rave’ dance parties. Of 96 individuals at raves in the Baltimore–Washington corridor who provided a saliva sample, 20% tested positive for ecstasy [15•]. They were more likely than nonusers or past users of ecstasy to have used marijuana and powder cocaine during the past year.

Circuit parties, which cater to gay and bisexual men, are another venue for use of ecstasy [16•,17•]. Some 72% of patrons at three major circuit parties had used ecstasy at such parties during the past year, and unsafe sexual behavior at the parties was associated with frequent ecstasy use [18]. Although known as the ‘love drug’, GHB can reduce libido and cause loss of erection [19,20], and so ‘party packs’ containing sildenafil (Viagra) and MDMA are available.

Most tablets containing MDMA are produced in Belgium and Luxemburg or in Asia. Locally produced ‘ecstasy’ tablets can contain other substances. Drug Enforcement Administration tests of large seizures of pills have found that all tablets contained some MDMA. In addition, some tablets were found to contain other controlled substances such as methylenedioxy-ethylamphetamine, methylenedioxy-amphetamine, amphetamine, methamphetamine, or ketamine. Some MDMA tablets (<1% of the total) were found also to contain other noncontrolled substances including caffeine, ephedrine, dextromethorphan, caffeine and ephedrine, ephedrine and dextromethorphan, or antihistamines such as diphenhydramine (Gauvin D, personal communication).

In comparison, single pills bought at the local level may not contain MDMA. Pills can be mailed in to a laboratory that analyzes contents; these are then posted on the DanceSafe website [21]. A review of the last 25 drugs tested in the mail-in category as of 27 October 2002 found that six contained only MDMA. Ingredients in the other 19 pills included methamphetamine, dextromethorphan, ephedrine, caffeine, methylenedioxy-ethylamphetamine, methylenedioxy-amphetamine, amphetamine, n-(3-trifluoromethylpheno) piperazine, benzyl-piperazine, guaifenesin, unidentified substances, or no drugs. DanceSafe also provides on-site testing of pills at raves and dance parties, but the on-site tests can only identify whether MDMA is present in the tablet; it cannot show whether other drugs, such as dextromethorphan, methamphetamine, or paramethoxyamphetamine, are also present.

Adverse effects

Common adverse effects of MDMA include agitation, anxiety, tachycardia, and hypertension; more serious adverse reactions include hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, renal failure, cardiac complications, intracranial hemorrhage, and hepatotoxicity [22,23••,24]. There is no antidote for MDMA, only supportive care similar to treatment for amphetamine or methamphetamine overdose [23••]. No withdrawal syndrome from MDMA has been reported [25••].

A review of 22 MDMA fatalities in New York City [26•] found that seven out of 13 that were due to acute

MDMA intoxication also involved cocaine and/or opiates; seven more were due to blunt trauma or gunshot wounds, and two were due to a combination of natural disease and drug intoxication. Other deaths attributed to 'ecstasy use' were actually caused by hyperthermia following ingestion of paramethoxyamphetamine – a drug packaged as ecstasy and that is mistakenly assumed to be a byproduct in the synthesis of MDMA (and MDMA is not produced in the synthesis of paramethoxyamphetamine) [27].

Adverse effects of ecstasy are also documented in admissions to substance abuse treatment programs. Admissions to programs funded by the Texas Commission on Alcohol and Drug Abuse (TCADA) for a primary, secondary, or tertiary problem with ecstasy increased from 63 in 1998 to 518 in 2002 [28]. Of the clients in 2002, the average age was 21 years, 64% were male, 61% were Anglo, 57% were involved with the criminal justice or legal systems, 20% had used needles to inject other drugs, and 43% had been in drug treatment before. The primary drug of abuse for these clients was ecstasy (24%), marijuana (33%), powder cocaine (11%), or amphetamines or methamphetamines (11%), or alcohol (10%).

In a different study of 173 adolescent persons and young adults interviewed with the Composite International Diagnostic Interview, Substance Abuse Module [29], 43% met the DSM-IV criteria for dependence on ecstasy and 34% met criteria for abuse of ecstasy. However, articles on evidence-based substance abuse treatment for persons seeking help for MDMA dependence do not appear to exist.

The incidence with which MDMA has been implicated in driving under the influence is increasing. However, there is no clear correlation between the blood concentration of MDMA and the specific demeanor of the individual [30].

Laboratory identification of MDMA is difficult. As many as one-third of immunoassay urine screens have failed to detect it in standardized specimens [16•], although some cross-reactivity with amphetamines may occur if the concentration is high. Toxicologists have now developed procedures for detection or quantification of MDMA and its metabolites [31••].

Long-term neurotoxic effects of MDMA, particularly in the serotonergic system, are not fully known. Studies in rodents and nonhuman primates, typically treated with higher dose MDMA, have demonstrated short-term and long-term central nervous system (CNS) neuronal damage with attendant reductions in serotonin [32]. Nonhuman primates exposed to several sequential doses

of MDMA in a regimen modeled after that used by humans developed severe brain dopaminergic neurotoxicity in addition to less pronounced serotonergic neurotoxicity. Recreational MDMA users may unwittingly be putting themselves at risk, either as young adults or later in life, for developing neuropsychiatric disorders related to brain dopamine and/or serotonin deficiency [33••].

Fox *et al.* [34•] found that initial cognitive deficits in ecstasy polydrug users may be more apparent in tasks known to be sensitive to temporal functioning. Users were significantly more impaired on a recognition task for complex visual patterns and spatial working memory as a function of task difficulty rather than systematic search strategy. They also exhibited a trend toward impairment on several learning paradigms. They remained relatively unimpaired on most measures associated with prefrontal functioning, with the exception of verbal fluency 'letter' generation.

A study of four groups (nonusers, novice users, regular users, and currently abstinent users of MDMA) [35] found evidence of impairments of verbal but not visual memory in MDMA users and that the deficits were not attributable either to differences in general reasoning ability or to impairment in working memory. The observed impairment may be attributable to a combination of reversible acute effects of MDMA resolving over a period of 2–3 weeks and more long-term changes associated with extent of lifetime consumption. Evidence has also been reported that MDMA use may be associated with deficits in executive function [36].

Studies have suggested that use of MDMA affects depression, other mood disorders, impulsiveness or hostility, psychotic symptoms, anxiety and panic disorders, and other psychopathologic disturbances. Selective impairments of neuropsychologic performance associated with regular ecstasy use have been found not to be reversed by prolonged abstinence, which is consistent with evidence that ecstasy has potent and selective neurotoxic effects on brain serotonergic systems in humans [37•]. A prospective, longitudinal study of mental disorders in ecstasy users [38•] found that users, as compared with nonusers, were at significantly increased risk for DSM-IV substance-related disorders and were at higher risk for alcohol use disorders than users of other illicit substances. They also had significantly higher rates for almost all DSM-IV mental disorders than did nonusers or users of other illicit drugs. However, the ecstasy use might be associated with use of multiple substances, and onset of mental disorder is more likely to precede rather than follow use of ecstasy and related substances. Heavy users have a

higher risk for developing psychiatric disorders, and polydrug use itself may lead to different types of psychobiologic problems, so it may be beneficial to assess the consequences of ecstasy use within the wider context of recreational drug use as a whole [39].

A review of studies of chronic recreational use of MDMA [40••] showed repeated use of ecstasy to be associated with sleep, mood, and anxiety disturbances, elevated impulsiveness, memory deficits, and attention problems that may persist for up to 2 years after cessation. In a subset of humans, particularly adolescent persons, depletion of serotonin by MDMA use may hasten or enhance vulnerability to a wide array of neuropsychiatric problems.

A study of 3634 conscripts entering military service in northern Spain [41•] found that MDMA users had more extensive drug abuse histories; also, those who had used MDMA in the year before the study had significantly higher scores on the Neuroticism and Psychoticism Subscales of the Eysenck Personality Questionnaire Adult Form and reported higher levels of sensation seeking. Another study [42] found that high novelty seeking scores were characteristic of ecstasy takers, which might predispose those individuals to ecstasy use initially.

Levels of past use of ecstasy affect psychological problems. In a web-based survey of 282 ecstasy users [43•], depression, memory problems, anxiety, mood fluctuation, poor concentration, infections, tremors/twitches, and weight loss were all significantly associated with the extent of ecstasy use. Memory problems attributed to ecstasy were reported by 19% of novice users, 52% of moderate users, and 73% of heavy users.

Former chronic ecstasy users who had not consumed ecstasy during the preceding 14 days had higher levels of depression than did their matched control individuals, and may be at risk with regard to the development of a more severe depressive syndrome [44].

Heavy ecstasy polydrug users reported significantly higher scores than did nondrug users on several Symptom Checklist-90 factors, including phobic anxiety, obsessive-compulsive behavior, anxiety, psychosis and somatization, and significantly higher rates of 'loss of sex or pleasure' [45]. These psychobiologic deficits were greatest in heavy ecstasy users and may reflect serotonergic axonal loss in the higher brain regions, especially the frontal lobes, temporal lobes, and hippocampus. These problems appear to remain long after the recreational use of ecstasy has ceased, suggesting that the neuropharmacologic damage may be permanent [46].

Research has also shown evidence of sex differences in the effects of MDMA. Equal doses of MDMA per kilogram body weight produced stronger responses in women than in men, which is consistent with an increased susceptibility of women to the serotonin-releasing effects of MDMA. Increasing doses of MDMA also produced more hallucinogen-like perceptual alterations, particularly in women [47]. Furthermore, women have also been found to be more susceptible than men to mid-week low mood following weekend use of MDMA; however, both men and women showed increased self-rated aggression. These results are interpreted in terms of an attenuation of serotonergic functioning for the period following acute use of MDMA [48•].

Reneman and coworkers [49,50•] reported heavy use of MDMA to be associated with neurotoxic effects on serotonin neurons, that women might be more susceptible than men, and that MDMA-induced neurotoxic changes in several brain regions of female ex-MDMA users are reversible. However, that study has raised questions among other researchers [51,52•–54•].

MDMA users are reported to be taking selective serotonin reuptake inhibitors such as fluoxetine or sertraline or antioxidants such as vitamin C or vitamin E to minimize their risks. Animal experiments suggest these substances may reduce serotonin depletion by MDMA, but they have not shown that they protect against brain damage [55] and selective serotonin reuptake inhibitors may block the metabolism of MDMA by the liver. Underground websites give specific information as to 'preloading' and 'postloading' and use of over-the-counter supplements such as 5-hydroxytryptophan, but this information does not appear to have been medically evaluated.

Methodologic criticisms

Most information used by ecstasy takers appears to come from nonscientific information on the Internet, with the methodologic problems inherent in studies of humans giving users a reason to discount the evidence amassed thus far. Some of these human studies have relied on patients to report both the extent and timing of MDMA use, and they have lacked control groups or were based on the assumption that participants in the studies would match control individuals before MDMA exposure.

Findings are complicated by the frequent use of other drugs (cannabis and amphetamines) that are known to be associated with cognitive impairment [56••], and this may confound studies of ecstasy users [57,58••]. Rogers *et al.* [59] found that everyday memory problems were related to cannabis use, with long-term prospective memory deficits related to past ecstasy use. Also,

Daumann *et al.* [60] suggested that psychologic problems may be less suitable functional indices of ecstasy-related neurotoxic damage of central serotonergic systems in humans than cognitive deficits.

Other questions have arisen regarding dosing in animal studies versus humans and the inability to test the effects of MDMA on non-drug-using humans. Controlled clinical trials would clarify these issues but legal, ethical, and clinical complications prevent or limit human studies of MDMA [32]. Cole *et al.* [61••,62••] provided an extensive critique of ecstasy studies and their methodologic difficulties, to which Morgan [63••], Croft [64••], and Parrott [65••] have replied.

γ -Hydroxybutyrate

GHB (sodium hydroxybutyrate, sodium oxybutyrate), a naturally occurring fatty acid found in mammals, is a CNS depressant that has intoxicating effects and, at sufficiently high doses, anesthetic properties [66]. It is known on the street by terms such as fantasy, liquid ecstasy, liquid X, grievous bodily harm, scoop, cherry meth, soap, salty water, organic quaalude, G, growth hormone booster, somatomax PM, gamma OH, and Georgia home boy. It is available as a powder or a solution.

One of its precursors, namely γ -butyrolactone (GBL), is converted to GHB by endogenous lactonases. GBL is used as an industrial solvent and has been marketed as a dietary supplement and cleaner for computer parts. Various brand names include Fire Water, Revivarant, Revivarant G, RenewTrient, GH Revitalizer, Verve, GH Release, Gamma-G, InvigorateX-Depress, Furomax, Insom-X, and Blue Nitro. GBL is a List I chemical in the USA, and requires documentation and justification of all purchases and sales. If intended for human consumption, GBL and related substances are regarded as controlled-substance analogs [23••].

Another precursor is 1,4-butanediol (1,4-BD), which is a Class I health hazard and is an industrial solvent sold to abusers under names such as (Revital)ize Plus, Serenity, Enliven, GHRE, SomatoPro, NRG3, Weight Belt Cleaner, Thunder Nectar, Pine Needle Extract, and Pine Needle Oil. It is metabolized in the body by alcohol dehydrogenase to GBL, which in turn is metabolized to GHB [23••], and this interconversion raises important issues for forensic scientists and law enforcement personnel [67].

Patterns of use and formulations

Since the 1980s, GHB has been used for its sedative and anabolic (body building) effects, but because of its intoxicating effects it became known as a club drug. In 1990, after reports of adverse events, the US Food and

Drug Administration ordered the removal of GHB from the market. GHB also produces anterograde amnesia and may cause victims to lose consciousness and be unable to resist or recall sexual assault. Because of its use to commit assault and its use as a club drug, it is now a Schedule I drug. However, GHB is a Schedule III drug when used under a Food and Drug Administration approved protocol to treat cataplexy in patients with narcolepsy. To minimize diversion, Orphan Medical, Inc., Minnetonka, Minnesota, is distributing Xyrem to users on a registry through a central pharmacy system rather than through local pharmacies.

GHB has been shown to alleviate withdrawal syndrome for alcoholic persons in European studies. In a double-blind comparative study of the effects of GHB and clomethiazole in ameliorating the symptoms of alcohol withdrawal, no difference was found in ratings of alcohol withdrawal symptoms or requests for additional medication [68•]. After tapering off the active medication, there was no increase in withdrawal symptoms, indicating that physical tolerance did not develop to either GHB or clomethiazole. Thirty-five alcohol-dependent patients who met the criteria for treatment resistance were given doses of GHB in an open 1-year study. [69] Sixty per cent completed the protocol, with 11.4% showing complete abstinence, 14.3% showing strongly reduced alcohol intake, and 34.3% still under treatment after a year.

At the December 2001 CEWG meeting [11], reports of use of GHB varied across the nation. In Boston it was reported to be a significant club drug, whereas in Chicago use was reported as infrequent and primarily among young Anglo males. In Denver it was reported as increasing in popularity, and in Los Angeles it was reported as increasing in popularity at venues other than clubs or raves. It was reported to be increasing in use and also as being used to commit sexual assault in St. Louis. Use in Texas centered in the Dallas–Fort Worth metroplex area.

In Australia, a study of GHB users found they were stable, highly educated, and well functioning [70••]. They had extensive experience with a range of drugs and typically used GHB with other drugs. However, even though the GHB users did not have a long or extensive experience with GHB use, 99% reported at least one negative side-effect. Over half (52%) reported becoming unconscious. The high rate of problems reported by a group with limited use of this drug suggests that, within the context of polydrug use, GHB is associated with significant risks to users.

DAWN emergency room mentions of GHB increased from 56 in 1994 to a high of 4969 in 2000, and then

declined to 3340 in 2001 (Fig. 1). Of the patients in 2001, 66% were male, they were older than patients admitted with a mention of ecstasy or ketamine (Fig. 2), and 73% were Anglo (the race/ethnicity of other patients was not reported). Seventy-four per cent mentioned other drugs with GHB: alcohol (54%), marijuana (14%), MDMA (12%), cocaine (5%), amphetamines (3%), and methamphetamines (2%) [14]. Note that because the DAWN case definition through 2002 requires intent to abuse, cases of sexual assault with GHB were not reported.

In 2002, 35 of the 48175 clients entering programs funded by the TCADA reported a primary, secondary, or tertiary problem with GHB, GBL, or 1,4-BD [28]. The average age was 31 years, 54% were male, 91% were Anglo and 9% Hispanic, 51% had been in treatment before, and 60% were involved in the criminal justice or legal systems. The primary problem drug at admission was GHB (34%), amphetamines or methamphetamines (20%), or crack cocaine (17%); 54% had a history of having used needles to inject drugs.

Illegal GHB and its precursors, GBL and 1,4-BD, can be obtained over the Internet and sometimes are marketed as solvents such as ink jet printer fluid or as GHB alternatives in health food stores, gyms, raves, and nightclubs. Chemistry kits, reagents, and recipes are available on the web to convert the precursors into GHB [66,71••], and GHB itself can be ordered from websites in some other countries.

Adverse effects

GHB and its precursors are often taken in combination with alcohol, which worsens respiratory symptoms and exacerbates CNS effects [72]. Likewise, use of GHB and a depressant drug can result in greater CNS depressant effects than are seen with either drug alone [66].

Illicit use of GHB has been associated with little consistency and precision in the doses consumed. An oral dose of 10 mg/kg has been reported to cause euphoria, amnesia, and hypotonia; doses of 20–30 mg/kg have resulted in somnolence within 15 min. Doses greater than 50 mg/kg result in unconsciousness and coma [25••,72].

The most serious effects of an overdose are sudden onset of coma and respiratory depression. Withdrawal from GHB can be complicated, especially if other drugs or alcohol are involved. The one distinguishing feature of GHB toxicity is the sudden awakening of the patient from a comatose state to a normal or hyperactivated state of arousal. Severe withdrawal reactions have been reported, with some dependent persons escalating their use to every 2–4 h in a pattern of around-the-clock

dosing [25••,56••,73–75]. Although these case studies show the abuse potential, there is little information on chemical dependency treatment. For some who use GHB or its precursors regularly, tolerance and dependence appear to build rapidly. Intervention and treatment efforts for GHB users are often delayed because many providers lack knowledge of symptoms of GHB intoxication and dependence. Information about GHB on the Internet and other lay sources may be misleading and imply that GHB is nonaddictive and has health benefits [56••].

Toxicological issues

Knowledge about the extent of abuse of GHB and its precursors has also been hampered by the lack of routine analytical methods for identifying GHB in tissues and fluids. They are not detected in routine urine screens but are reliably detected by specific requests for GC–MS. Timing is important because GHB is rapidly excreted as carbon dioxide through exhalation [25••]. GHB is virtually undetected in the urine 12 h after ingestion [23••].

Immunoassays for GHB or GBL are not available [31••]. Couper and Logan [76] reported 13 cases in which GHB was identified in the blood of individuals arrested for impaired driving in Washington State. It should be considered and tested for when drivers exhibit symptoms of CNS depression that are not accounted for by alcohol or other drugs, or where the drivers exhibit a tendency to fall asleep or lose consciousness during investigation.

GHB can be produced either as a pre-mortem or post-mortem artifact. Post-mortem GHB production occurs even in stored ante-mortem blood samples (if preserved with citrate). It is unwise to draw any inferences about causality unless blood and urine are both analyzed and levels are found to be elevated, the blood is collected in NaF-containing tubes, and a detailed case history is obtained. It is the policy of the US Federal Bureau of Investigation laboratory to report only ‘positive’ GHB results when substantial amounts of GHB are found in the urine as well as in the blood [77]. GHB has also been found to distribute into the hair root bulb [78].

A sensitive and specific GC–MS method using selective ion monitoring has recently been developed for the quantification of GHB in blood. This method uses liquid–liquid extraction and disilyl derivatization, without conversion to GBL, followed by GC–MS analysis using GHB-d₆ as the internal standard. It is sensitive in that it requires a sample of only 50 ml [79].

Ketamine

Ketamine, a derivative of phencyclidine hydrochloride, is an anesthetic that has been approved for human and

animal use, both in trauma and emergency surgery as well as veterinary medicine. Ketamine is also known as special K, vitamin K, K, kit-kat, keets, super acid, super k, and jet.

Ketamine is a Schedule III controlled substance and is available in powder and tablet forms as well as an injectable formulation. It is difficult to manufacture and most abusers acquire it through diversion of the prescription product or theft from veterinary supplies. The elimination half-life is approximately 2 h. Anesthesia doses are 2–10 mg/kg whereas recreational doses can range between 50 and 100 mg [10••].

The number of mentions of ketamine in the DAWN emergency room system increased from 19 in 1994 to 679 in 2001; however, as Fig. 1 shows, the number of mentions of ketamine was much lower than that for other club drugs. Estimates for ketamine by age group were too imprecise for publication in 2001, but in 2000 83% were male; 76% were Anglo, 4% Hispanic, and 3% African-American; and 65% were aged between 18 and 25 years (Fig. 2). Of patients mentioning ketamine in 2001, 74% also mentioned concurrent use of other drugs: alcohol (33%), heroin (17%), cocaine (14%), marijuana (12%), methamphetamine (10%), LSD (8%), GHB (2%), and amphetamines (1%) [14]. There were no ketamine admissions to TCADA treatment programs in 2002.

At the December 2001 CEWG meeting [11], ketamine was reported popular in the club and rave scene. In Washington, DC, it was reported to be a common intoxicant in these scenes, and injecting the drug might be increasing at 'after hours' parties and other alternative venues. In St. Louis, thefts of ketamine from veterinarians were increasing.

A study of gay and bisexual males attending circuit parties found that over 60% had used ketamine at parties during the past year and the relationship with unsafe sexual behavior was significantly associated with frequent use of ketamine [18].

Frequent users often take ketamine in a pattern of cyclical binges similar to cocaine or amphetamine dependence, and users can become psychologically dependent, with craving and a high tolerance, but no evidence of a physiologic withdrawal syndrome [80]. At high doses, it can cause delirium, amnesia, impaired motor function, high blood pressure, depression, and potentially fatal respiratory problems. Low dose effects are described as 'mild, dreamy, floaty, and slightly outside their bodies'. Higher doses produce hallucinogenic 'trippy' effects that makes one seem far away from one's body, and reaching the 'K-hole' is described as being a near-death experience that can be frightening or

'spiritually significant', according to websites. Flashbacks can recur days or weeks after use [56••].

No antidote exists for ketamine; management is supportive care with special attention to cardiac and respiratory functions [23••]. Once detoxified, one treatment protocol recommends following the model used for cocaine and amphetamine dependence, with abstinence from all drugs from day 1. As with stimulant dependence, the therapist should avoid confrontation because the likelihood of the person's dropping out is very high. Relapse prevention involves discovering what situations and triggers occur before taking the steps that lead to relapse so that alternative responses can be developed [80]. Additional studies are needed to gain a better understanding of the extent of ketamine abuse and dependence and to identify symptoms of withdrawal and effective treatments [56••].

Ketamine is not detected in routine drug screens, and clinicians should be aware that immunoassays for phencyclidine may cross-react with ketamine assays [23••]. High-performance liquid chromatography is required to detect it reliably [10••].

Long-term cognitive or neuropsychiatric effects have not been sufficiently studied in ketamine users [56••]. Earlier studies found that chronic abuse of ketamine may be associated with persisting impairment of memory and other cognitive function in humans, although it may not affect attentional processes or spatial memory but may interfere only selectively with cognition. A study of rhesus monkeys found that ketamine interferes with multiple aspects of cognition at subanesthetic doses [81•]. As with other club drugs, drug challenge investigations of the effects of ketamine in humans are limited by ethical concerns.

Rohypnol

Rohypnol (flunitrazepam) is a benzodiazepine that was originally formulated for preoperative anesthesia or sedation and treatment of insomnia. At low doses, flunitrazepam acts as a muscle relaxant and a sedative/hypnotic. At higher doses, it can cause lack of muscle control and loss of consciousness. Because it was specifically formulated to produce anterograde amnesia, it has been used to commit sexual assault.

Street names include roofies, la rocha, roche, R2, rope, forget-me pill, run trip and fall, los dos, and Mexican valium. The number of mentions in DAWN emergency departments peaked in 1996; by 2001, the numbers were too imprecise to be considered reliable [14].

In 1998 there were 247 persons admitted to programs funded by TCADA who had a primary, secondary, or

tertiary problem with Rohypnol. By 2002, 365 persons were admitted with the same problems. In 2002 the average age was 18 years, 74% were male, 95% were Hispanic, and 69% were involved with the legal or criminal justice system. Some 82% of these clients were from the border area. The primary problem drugs were marijuana (49%), Rohypnol (15%), powder cocaine (13%), heroin (8%), alcohol (7%), and crack cocaine (6%) [28].

Rohypnol was originally formulated in 1 mg and 2 mg tablets. Since 2001, only the 1 mg tablet manufactured by Roche, Basel, Switzerland, has been available, although generic products continue to be available in the 2 mg strength, which has been the strength preferred by abusers [82*]. Although the generic pills continue to be white and round, Roche has reformulated the 1 mg pill to be a grayish-green oval tablet. In an attempt to deter sexual assault, it now contains a dye that will turn blue in liquid. Sexual predators are now using blue punches and blue fruit drinks [28].

Rohypnol has never been approved for use in the USA, and since 1996 it has been illegal to bring the drug into the USA. Other countries, such as New Zealand, Australia, and Sweden, have now prohibited or limited its use, but it remains available elsewhere and continues to be illegally imported. In 2002, Texas students in grades 7–12 who lived on the Texas–Mexico border reported 10.9% lifetime and 4.4% past month use of Rohypnol, as compared with 3.8% lifetime and 1.3% past month use by students not living on the border [28].

Adverse effects include hypotension, dizziness, confusion, visual disturbances, urinary retention, and, in some users, aggressive behavior. Acute patient management is supportive care and attention is given to the possible ingestion of other CNS depressants [23**].

Studies of juvenile delinquent populations have found flunitrazepam abuse can lead to serious violent behavior in these groups and in subjects characterized by vulnerable personality traits [83*]. This effect is confounded by the concurrent use of alcohol or other drugs [84]. It is also abused because it reinforces the depressant effect of heroin and blunts the ‘crash’ after the use of cocaine [85*].

Rohypnol has been found in driving under the influence cases [84] and, although a standard component of most urine drug screens is testing for benzodiazepines, flunitrazepam is administered in such small amounts and distributed so rapidly that detection methods commonly fail. Samyn *et al.* [85*] reported a method for onsite screening for flunitrazepam in oral fluids that could detect the drug within 6 h of use, but the screen

should be confirmed. Typical toxicologic tests can only detect flunitrazepam in blood and urine for up to 72 h after injection because of quick metabolism and elimination. Because persons who have been sexually assaulted may not report the crime for days or weeks, Negrusz *et al.* [86] tested hair samples for flunitrazepam and found good support for the use of forensic hair testing in the case of flunitrazepam-facilitated sexual assault.

Conclusion

Club drug use has been conceptualized as a very simple phenomenon that involved dancing at raves and taking drugs. A closer examination of the published literature has shown that each drug has different properties and, often, different users in different settings. Each drug has different adverse effects and requires different acute care protocols. Even though the club drug phenomenon was identified early, scientific information about these drugs, their identification, and short-term and long-term effects are still evolving. The lack of research-based information on the adverse effects of these drugs has led to the emergence of a range of web-based sites that may or may not provide accurate information, and the limitations on research in humans has meant that some findings can be discounted by users. Effective chemical dependency treatment protocols for each of these drugs are still needed.

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